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Long-Term Outcomes of Myeloablation and Autologous Transplantation of Relapsed Acute Myeloid Leukemia in Second Remission: A British Society of Blood and Marrow Transplantation Registry Study

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ABSTRACT

Relapsed acute myeloid leukemia (AML) in adults has a poor prognosis if treated with chemotherapy alone. Case series have previously supported the role of myeloablation and autologous transplantation as a potentially curative treatment. This study aimed to use the large numbers and extended follow-up data in the British Society of Blood and Marrow Transplantation (BSBMT) registry database to establish long-term outcomes and relate these to biological and procedural factors. The BSBMT registry database was used to retrospectively identify 152 adult patients (age, 16–69 years) with AML in second remission treated with autologous transplantation in 1982–2003. Cytogenetic data were available for 68% of the patients; of these, at diagnosis, 42% had good risk features, 57% had standard risk features, and 1% had poor risk features. Conditioning regimens varied; autologous rescue was provided with bone marrow (BM) (71%), peripheral blood stem cells (PBSCs) (18%), or both (11%), which were harvested during first complete remission (CR1) and/or second CR (CR2). Median follow-up was 84 months (range, 2–200 months). At 10 years, actuarial overall survival (OS) was 32%, progression-free survival (PFS) was 28%, and relapse rate (RR) was 57%. The 100-day nonrelapse mortality (NRM) was 7%, rising to 11% at 1 year and to 14% at 10 years. OS was significantly related to M3 subtype (5-year OS, 66%; $P = .005$), patient age at diagnosis ($P = .005$) and transplantation ($P = .026$), and length of CR1, with greatest significance if the patient was dichotomized at CR1 duration of < 8 months or ≥ 8 months ($P = .0001$). There was no difference in OS between regimens containing total body irradiation (TBI) and chemotherapy alone ($P = .7$). In relation to the nature of autologous graft material, there was improved OS ($P = .025$) and PFS ($P = .009$) with the use of cells harvested entirely in CR1 compared with cells harvested in CR2 or in both CR1 and CR2. Engraftment times were significantly shortened with the use of PBSCs alone or in combination with BM compared with BM alone ($P = .0001$), but there was no significant long-term impact on OS, PFS, RR, or NRM. This study provides long-term follow-up data in one of the largest series of patients with standard-risk and good-risk AML in CR2 treated with autologous transplantation and supports earlier observations that long-term survival is achievable in about 1/3 of patients overall and in about 2/3 of patients with M3 with a relatively low NRM. Outcomes are better in patients with CR1 ≥ 8 months by use of grafts obtained entirely in CR1 and use of PBSCs. TBI conditioning did not confer an advantage. Randomized studies against unrelated donor transplantation are warranted.
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KEY WORDS

Autologous transplantation • Relapsed acute myeloid leukemia

INTRODUCTION

Despite improvements in the treatment and prognosis of acute myeloid leukemia (AML) in recent years, disease relapse continues to affect most patients [1,2]. After relapse, a range of treatment options is available, ranging from intensive treatments to palliative and supportive treatments. The choice of treatment pathway depends on a number of variables, including the patient's functional status and age, leukemia risk group, ability to induce a second remission (CR2), and the availability of allogeneic donors.

Although CR2 may be achieved in a significant proportion of patients with chemotherapy alone, long-term survival is limited (eg, a 3-year survival rate of 8%–18%) unless transplantation is performed [3]. The availability of matched sibling donors is limited, and although matched unrelated donors (MUDs) are available for some, the risks of allogeneic transplantation may be considered too great in many patients. Autologous transplantation presents an alternative means of delivering myeloablative treatment in relapsed AML and has been associated with lower risk of treatment-related mortality (TRM). Although the risk of infusing leukemic cells has been demonstrated [4], a number of limited case series have supported long-term remission after autologous transplantation in AML in the salvage setting, with durable CR2 in 25%–46% of patients overall in relapsed AML [5-9] and in > 50% of those with acute promyelocytic leukemia [10,11].

We used the British Society of Blood and Marrow Transplantation (BSBMT) registry to identify cases of relapsed AML treated with autologous transplantation in CR2 between 1982 and 2003. The aim of this study was to use the data from this large group of patients with long-term follow-up to retrospectively analyze the long-term outcomes of autologous transplantation as a consolidation treatment for AML in CR2, and to relate outcome to demographic, disease-related, and procedural aspects of treatment.

METHODS

Patient Identification

This was a retrospective, observational study. Patients age 16 or older with a diagnosis of AML who had received an autologous transplantation in CR2 were identified from the BSBMT database. Also included are 6 patients with AML diagnosed when they were age < 16 years (median age, 15 years; range, 11–15 years). Transplantation units in the United Kingdom are required to report basic transplantation and demographic data to the BSBMT. A total of 152 patients were identified from 28 participating centers. All centers were contacted to verify the data already contained in the BSBMT database and to collect non-standard data, including cytogenetics, harvesting information, and details of conditioning regimens. The study was approved by the BSBMT Clinical Trials Committee and the National Health Service (NHS) Research and Development Department of Sheffield Teaching Hospitals NHS Trust.

Table 1. *Patient Characteristics (n = 152)*

Age at diagnosis, median (range)	**45.3 (11.2–67.7)**
Sex (M), n (%)	**84 (55%)**
FAB class, n (%)	
M0	**3 (2%)**
M1	**19 (15%)**
M2	**29 (22%)**
M3	**28 (22%)**
M4	**31 (24%)**
M5	**14 (11%)**
M5a	**1 (1%)**
M6	**4 (3%)**
Unknown	**23**
Risk group, n (%)	
Good risk	**42 (42%)**
Standard risk*	**56 (57%)**
Poor risk	**1 (1%)**
Unknown risk	**53**
Length of CR1, median (range)	**500 days (24–2496)**
Follow-up, median (range)	**2559 days (65–6094)**

*Standard risk = standard risk cytogenetic abnormalities + normal cytogenetics.

Patient Characteristics

Detailed patient characteristics are given in Table 1. A total of 152 patients in CR2 of relapsed AML received an autologous transplant between 1982 and 2003. The median age at diagnosis was 45.3 years (range, 11.2–67.7 years) and that at transplantation was 47.4 years (range, 16.1–69.6 years); the sex ratio was fairly equal (55% male). Length of first remission (CR1) ranged from 24 days to 2496 days (6 years, 10 months), with a median of 500 days. A total of 42 patients had a CR1 duration of < 1 year. Median follow-up was 84 months (range, 2–200 months).

Cytogenetic data were available for 104 patients (68%) at diagnosis; 44% of these patients had normal cytogenetics. The available cytogenetic data showed that the group comprised 42% good-risk, 57% standard-risk, and 1% poor-risk patients, based on the risk group stratification of the Medicine Research Council (MRC) AML trials [12].

CONDITIONING REGIMENS AND SOURCES OF STEM CELLS

Of the 143 patients for whom the conditioning is known, 76% had chemotherapy-alone conditioning and 24% had total body irradiation (TBI)-based conditioning. The 2 most common regimens, accounting for 70% of the procedures, were busulphan and cy-

clophosphamide (BuCy) and cyclophosphamide and TBI (Cy TBI). Other regimens included melphalan and etoposide. Most patients were supported with autologous bone marrow (BM) alone (n = 108; 71%); others were supported with peripheral blood stem cells (PBSCs) alone (n = 27; 18%) or a combination of BM and PBSCs (n = 17; 11%) (Table 2).

Study End Points and Definitions

Analysis of engraftment, early (100 day) and late (10 year) nonrelapse mortality (NRM), relapse risk (RR), progression-free survival (PFS), and overall survival (OS) were performed. Data was also analyzed with respect to FAB class, cytogenetics, risk stratification, duration of CR1, conditioning regimen, and stem cell source. Engraftment was defined as days to neutrophil recovery $> 0.5 \times 10^9$/L sustained over 2 days.

Statistical Analysis

All statistical analyses were performed using R [13]. OS and PFS were calculated by the Kaplan-Meier method, and univariate comparisons were made using the log-rank statistic for binary or categorical comparisons and using Cox's proportional hazard regression for ordered multiple comparisons (eg, age group or year of transplantation) [14]. NRM and RR were treated as competing risks and compared using cumulative incidence [15]. *P* values $< .05$ were considered significant.

Table 2. *Conditioning Regimens, Sources of Stem Cells, and Timing of Harvest*

Age at transplantation, median (range)	**47.4 (16.1–69.6)**
Conditioning, n (%)	
TBI	**35 (24%)**
CyTBI	**28 (20%)**
MelTBI	**2 (1%)**
BuCyTBI	**2 (1%)**
Unknown	**3 (2%)**
Chemotherapy alone	**108 (76%)**
BEM	**18 (13%)**
BuCy	**73 (51%)**
Busulphan	**2 (1%)**
BuMel	**1 (1%)**
Melphalan	**1 (1%)**
BEAM	**1 (1%)**
Unknown chemotherapy	**12 (8%)**
Unknown	**9**
Source of stem cells, n (%)	
BM	**108 (71%)**
PBSC	**27 (18%)**
BM + PBSC	**17 (11%)**
Timing of harvest, n (%)	
CR1	**74 (60%)**
CR2	**41 (33%)**
Both	**9 (7%)**
Unknown	**27**

Table 3. *Response to Transplantation (n = 152)*

Engraftment, n (%)	
Yes	**140 (95%)**
No	**8 (5%)**
Unknown	**4**
Time to engraftment, median (range)	**21 (8–115)**
BM	**27 (8–115)**
PBSC or both	**15 (9–40)**
***P* value (BM vs PBSC or both)**	**<.0001**
Current status, n	
Alive	**52**
CR2	**45**
CR≥3	**5**
Relapse	**2**
Unknown	**0**
Dead	**100**
Relapse	**78**
Transplant-related	**21**
Unknown	**1**
Survival after transplantation*	
Median (95% confidence interval)	**468 days (385-945)**
OS at 1 year	**59%**
PFS at 1 year	**50%**
OS at 5 years	**32%**
PFS at 5 years	**30%**
OS at 10 years	**32%**
PFS at 10 years	**28%**
Late deaths (>10 years)	**3**
Multiorgan failure,transplant-related	**1**
Liver failure due to sepsis, not transplant-related	**1**
Unrelated clinical condition	**1**
NRM†	
100 days	**7%**
1 year	**11%**
10 years	**14%**
Progression or RR†	
100 days	**15%**
1 year	**38%**
10 years	**57%**

*Kaplan-Meier estimates.
†Calculated as competing risks by cumulative incidence.

RESULTS

OS, PFS, RR, and NRM rates are given in Table 3. Both the 5-year and 10-year OS were 32%. The 5-year PFS was 30%, and the 10-year PFS was 28%. OS declined from time of transplantation to 5 years and plateaued between 5 and 10 years. OS and PFS survival curves closely correspond (Figure 1). Of the 152 patients, 7% had died of NRM before day 100; by 10 years, the NRM had risen to 14%. There were 3 nonrelapse deaths after 10 years, 1 due to transplantation-related multiorgan failure and 2 considered unrelated to transplantation. Most relapses occurred within the first 2 years. Of those who relapsed, the median time to relapse was 185 days. The last relapse in the study period occurred 7.7 years after autologous transplantation. A total of 18 patients remain alive and progression-free beyond that time, providing a reasonable indication of plateau. Figure 2

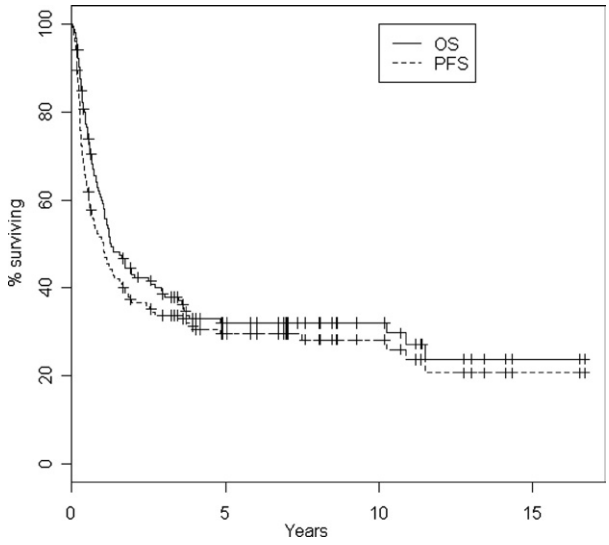

Figure 1. OS and PFS.

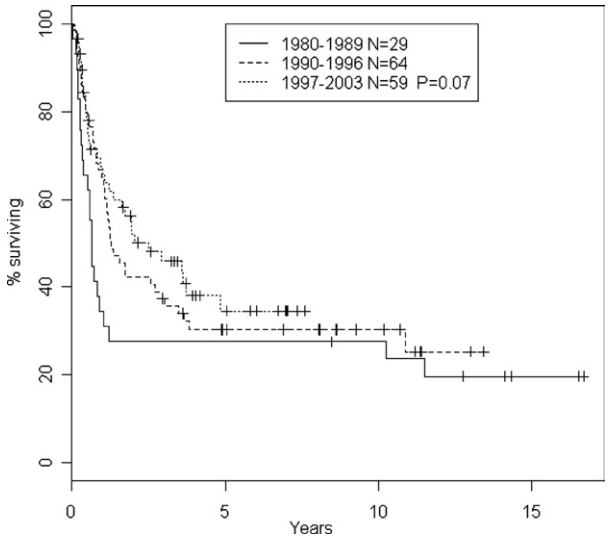

Figure 3. OS by year of transplantation.

shows a cumulative incidence plot of RR and TRM. Survival data were analyzed for 3 cohorts: 1982–1989, 1990–1996, and 1997–2003. Although there was a mild trend to better survival over time, as would be expected with improved transplantation procedures, the *P* value of .07 was not significant (Figure 3).

Cytogenetics and FAB Type

OS at 5 years was 58% for the good-risk group, 29% for the standard-risk group ($P = .02$), and 0% for the poor-risk group (although only 1 patient included in this study was designated as poor risk). Figure 4 shows OS by risk group, with good risk separated into M3 and others [inv16/t(8;21)] and compared with standard risk. OS at 5 years in patients with FAB-type M3 compared with other good-risk patients, standard-risk patients, and poor-risk patients was 66%, 42%, 29%, and 0%, respectively ($P = .008$; *P* refers to a 4-way comparison).

Length of CR1

To establish the duration of CR1 that resulted in the greatest difference in survival, patients were dichotomized into groups with CR1 greater or less than defined posttransplantation periods, and the highest degree of statistical significance was established. Patients with CR1 of ≥ 8 months had the most significantly improved OS (1-year OS of 66% vs 31%; $P = .0001$). There were no long-term survivors in the group with CR1 < 8 months, but for patients with

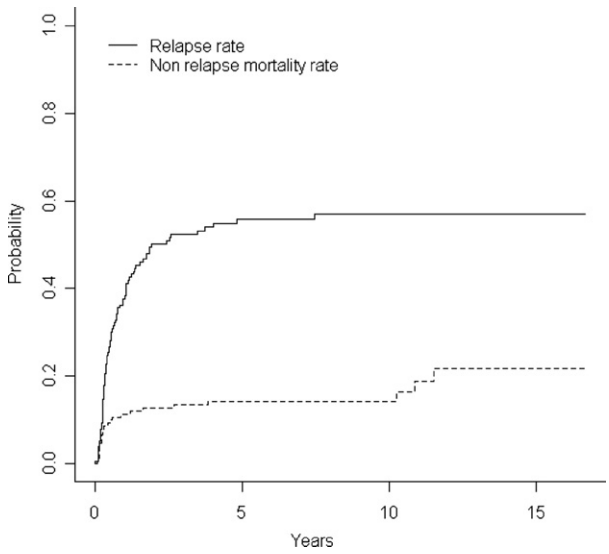

Figure 2. Cumulative incidence plot of RR and NMR. Three patients died more than 10 years after transplantation; 1 due to respiratory failure attributed to TBI-induced lung fibrosis and the other 2 unrelated to treatment or relapse.

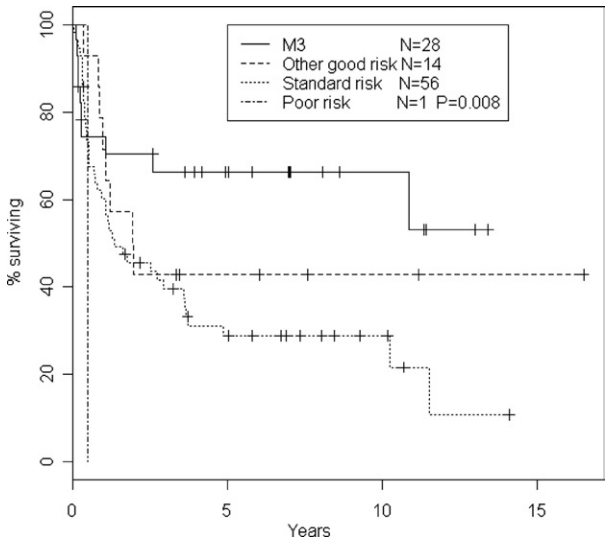

Figure 4. OS by risk group; good risk separated into M3 and others [inv16/t(8;21)] compared with standard risk.

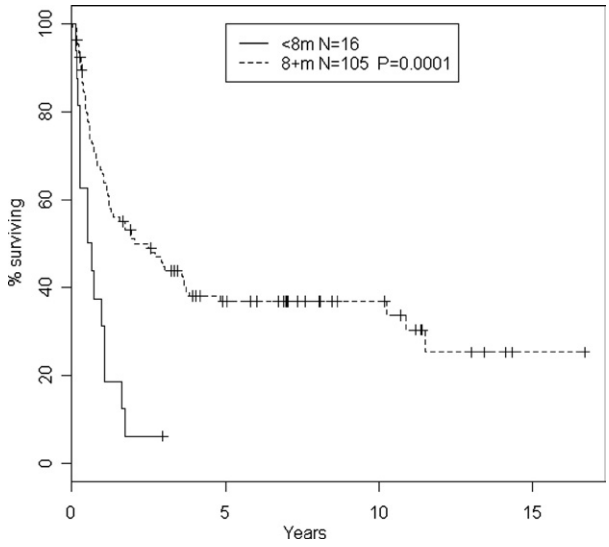

Figure 5. OS by duration of CR1.

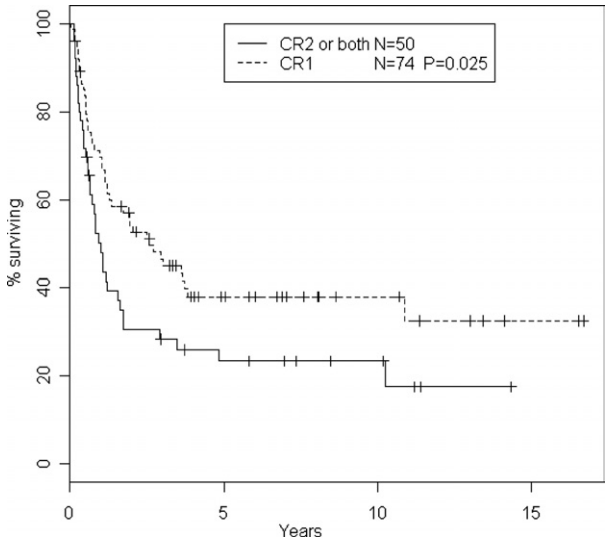

Figure 7. OS by timing of harvest.

CR1 > 8 months, OS at 5 and 10 years was 37% (Figure 5). Dichotomizing the patients into those with CR1 of < 12 months and > 12 months also yielded significant results, with 5-year OS of 23% versus 10-year OS of 38% ($P = .02$).

Patient Age

OS was significantly better in younger patients. Considering age at diagnosis, OS was 52% in patients age < 30 years, 35% in those age 30–49 years, and 17% in those age > 50 years ($P = .005$). Similarly, considering age at transplantation, OS was 45% in patients age < 30 years, 37% in those age 30–49 years, and 22% in those age > 50 years ($P = .026$) (Figure 6).

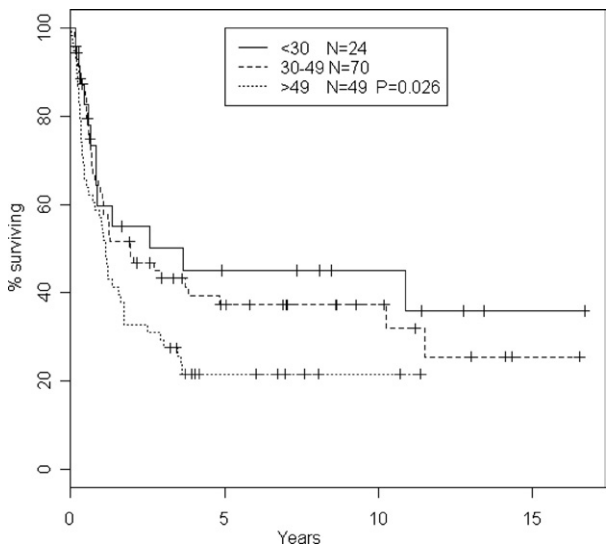

Figure 6. OS by age at transplantation.

Conditioning Regimen

No significant difference in OS at 5 years was found between patients treated with TBI-based or chemotherapy-only conditioning regimens: 32% versus 33% ($P = .7$). Late nonrelapse deaths occurred in both groups.

Time of Harvest

OS was improved when the stem cell harvest used was obtained entirely within the CR1 compared with harvest obtained during CR2 (38% vs 23%; $P = .025$) (Figure 7). PFS also was significantly improved with entire CR1 harvest compared with CR2 harvest (35% vs 22%; $P = .009$). There were no significant differences in RR and TRM between the 2 groups.

Source of Stem Cells

Neutrophil engraftment of $>0.5 \times 10^9$/L for at least 2 consecutive days was achieved in most patients where recorded (94%). The median time to engraftment was 21 days (range, 8–115 days). As expected, median time to engraftment using PBSC ± BM was quicker at 15 days, compared with 27 days using BM alone ($P = .0001$). There were no significant differences in OS, PFS, RR, and NRM based on the source of autologous rescue comparing BM alone and PBSC ± BM ($P = .64$). Data relating to platelet engraftment time were not available.

Multivariate Analysis

Multivariate analysis was performed using Cox's proportional hazard regression. Considering OS, length of CR1 remission < 8 months ($P = .00012$) and MRC risk group stratification ($P = .01$) were identified as significant independent variables. For PFS, the same 2 variables—length of CR1 > 8 months ($P =$

.0001) and MRC risk group ($P = .004$)—were identified as significant.

DISCUSSION

This retrospective study summarizes a national experience of autologous transplantation as a consolidation treatment in adult patients with AML who have relapsed but have achieved CR2. As with any retrospective study, it may be susceptible to selection bias. For example, the criteria for patient selection are not predefined, and clinicians may have selected only fitter patients from standard-risk and good-risk cytogenetic prognostic groups for the procedure. Indeed, because < 50% of patients achieve CR2 [3], the fact that these patients had achieved CR2 introduces a favorable degree of bias, and the results of this study should not be taken as outcomes of salvage of relapsed AML overall.

Nevertheless, this is one of the largest series considered to date. It has a long follow-up period and provides a reference for outcome data in the United Kingdom. Although there were trends showing improved OS, PFS, and NRM over time (presumably related to better supportive care and greater experience), these were not statistically significant. These observations, and the fact that the practice of autologous transplantation in AML has changed relatively little over time, indicate that it is reasonable to draw conclusions for application to current clinical practice on long-term data from the last 2 decades.

The 5-year OS of 32% demonstrates that autologous transplantation is a valid therapeutic option for adults with relapsed, standard-risk, and good-risk AML who achieve CR2 and confirms the results of similar retrospective studies with disease-free probabilities of 30%–35% [7,8]. In our study, the results apply to a broad age range of patients (age 16–69 years) and were achieved with a relatively low NRM (7% at 100 days and 14% at 10 years). This compares favorably with rates reported in other studies, which range from 4% to 27% [5,6,16].

This study confirms that outcome for autologous transplantation in acute promyelocytic leukemia is particularly good, with approximately 2/3 of patients achieving prolonged survival. This compares favorably with outcomes from therapy with specific agents, such as ATRA and arsenic trioxide [10,11]. Given the toxicity associated with allogeneic transplantation, autologous transplantation may be the best treatment option for patients with acute promyelocytic leukemia in CR2. Our findings also confirm the improved outcome in younger patients and those with CR1 > 8 months in whom adequate autologous harvests were collected during CR1.

The findings of this study provide information to help optimize the use of autologous transplantation. Clearly, patients with M3 benefit the most, although moderately successful outcomes were achieved in those with standard-risk disease. Autologous transplantation is best restricted to patients with CR1 > 8 months. Interestingly, although TBI has been considered advantageous in treating AML, the survival curves for treatment with and without TBI were almost identical. The choice of myeloablative treatment may be best based on which treatment will likely minimize toxicity. Moreover, in many units, chemotherapy-only conditioning will be advantageous because of the limited and restricted scheduling of TBI.

In relation to the choice of autologous rescue, our findings suggest that outcomes are best if the harvest used is obtained entirely during CR1, with collections of PBSCs forming at least part of the graft. Why outcomes are superior with harvests obtained during CR1 is unclear, but it may be related to less contamination or perhaps to more chemosensitive disease, less dysplasia, or other biological factors associated with the leukemia. Nevertheless, although collection of a full PBSC harvest during CR1 may be difficult, the suggestion of superior outcomes in this study may justify a more systematic and aggressive approach to harvesting during CR1, with a combination of multiple PBSCs combined with BM harvesting when necessary. Although relatively few patients in this study received PBSCs (27%), autologous rescue now routinely contains a PBSC component, suggesting that a prospective analysis will demonstrate further improvements in outcome.

Despite the results of this study of autologous transplantation, HLA-matched sibling allogeneic transplantation with myeloablative conditioning is likely to remain the treatment of choice for relapsed AML in CR2 when available [17]. However, its applicability is restricted by donor availability and also by the age and fitness of patients. Recently reported results from the UK MRC comparing HLA-matched sibling allogeneic transplantation, MUD transplantation, and autologous transplantation in AML CR2 reported 5-year OS of 54%, 40%, and 33%, respectively [18]. These figures provide a useful comparison to the data of the present study but may not be entirely comparable, because of the tendency for MUD transplantation to be limited on grounds of tolerability to younger patients, in whom outcomes with autologous transplantation are better than average (eg, patients age < 30 years had a 5-year OS of 45% with autologous transplantation). Moreover, MUD transplantation is complicated by higher rates of graft-versus-host disease, increased susceptibility to infection, reduced quality of life, and increased risk of late death, especially in older patients. The financial costs are also considerably higher for MUD transplantation compared with autologous transplantation.

Recently reported results of an international retrospective analysis of autologous transplantation ver-

sus MUD transplantation for AML in CR1 and CR2 reveal adjusted 3-year survival probabilities of 57% (53%–61%) after autologous transplantation compared with 44% (37%–51%) after MUD transplantation in CR1 and 46% (39%–53%) after autologous transplantation and 33% (28%–38%) after MUD transplantation in CR2 [9]. The authors of that study noted that although relapse was less frequent with MUD transplantation, the high TRM offset the superior antileukemia effect of MUD transplantation.

Reduced-intensity transplantation is another therapeutic option for treating relapsed AML that offers a potentially curative graft-versus-leukemia effect and considerably lower NRM, thus expanding the number of potential recipients [19]. OS rates of 30%–50% have been reported [20-25]. Therefore, a prospective trial comparing autologous transplantation with MUD transplantation and/or reduced-intensity transplantation may be reasonable and would provide the opportunity to address practical issues unresolved by this and other analyses, including decisions related to patient age and economic issues. The design and selection criteria of a prospective trial would require careful consideration. Elderly patients and those with poor-risk cytogenetics are unlikely to benefit from autologous transplantation. However, for younger patients and those with standard-risk or good-risk cytogenetics, the superior treatment option is not yet clearly established. A prospective trial with 3 arms comparing autologous transplantation, MUD transplantation, and reduced-intensity transplantation would address this issue.

Outcomes of autologous transplantation also may be improved if this therapy were combined with current developmental approaches. Given the possibility that reinfused cells are the source of relapse [4], previous studies have investigated purging techniques. Many of these studies have used relatively crude techniques (eg, ex vivo chemotherapy) for purifying the autologous graft [7,26] and have failed to show a benefit. More sophisticated biotechnology now exists, which may result in more effective decontamination without compromising graft function [27].

It may be reasonable to consider myeloablation and autologous transplantation as a relatively safe but profound debulking treatment, after which minimal residual disease could be eliminated using pharmacologic or immunologic "maintenance" therapies. Many novel agents for treating AML are currently under investigation, some of which may be more effective as maintenance therapies directed at minimal residual disease posttransplantation. Reduced-intensity transplantation may be more effective if used as cellular immunotherapy against MRD after autologous transplantation. Combined autologous and reduced-intensity allogeneic transplantation has been shown to be feasible for treating various diseases [28].

In conclusion, autologous transplantation should remain a routine option in the treatment of patients with relapsed AML, particularly those with M3 and those with standard-risk disease when there no HLA-matched sibling donor is available. Consideration should be given to harvesting during CR1 in patients lacking an allogeneic donor. Avenues may be available to improve outcome by incorporating new biotechnological, pharmacologic, and cellular immunotherapy approaches. Prospective comparison with MUD transplantation and reduced-intensity transplantation would provide further evidence on which to base the choice of treatment.

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